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Running head: Targeted drugs in Hodgkin lymphoma

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ABSTRACT

Treatment of classical Hodgkin lymphoma (cHL) has been a success story, with cure of localized disease with radiotherapy in the 1930s, cure of advanced stages with combination chemotherapy +/- radiotherapy in the mid-1960s and continuous improvements since then. Despite this approximately 2% of cHL patients (in the pre-targeted drug era) are primarily refractory to conventional therapy with only 50% becoming long-term survivors and another 13% relapse with only 60% being alive 10 years post-recurrence (exemplified in Swedish 18-65 year old patients diagnosed 1992-2009).

Recently novel targeted drugs were approved for refractory/relapsed HL and we here review results of trials underlying these approvals and new trials follow this. In summary, Brentuximab vedotin can be used in refractory patients as a complement to high-dose chemotherapy with autologous stem cell transplantation (SCT) improving the chances to proceed to an allogenic SCT and cure, as consolidation after autologous SCT and as palliative life-prolonging treatments in other patients. However, we have yet to define if this drug provides its best benefit in first-line, second-line, as consolidation and/or in refractory disease/relapse.

Trials of immune checkpoint inhibitors, such as those targeting program death 1 (PD1) (nivolumab/pembrolizumab), and thus not primarily the tumor cells, report overall response rates of >65%. Long-term results and phase III trials are still lacking, but nivolumab recently gained approval in refractory patients already treated with brentuximab vedotin and autologous SCT. Other novel treatments of interest include T-cells with a chimeric antigen receptor (CAR T-cells) and combination therapies with histone deacetylase (HDAC) inhibitors.

INTRODUCTION

The incidence rates of classical Hodgkin lymphoma (cHL) range from less than 0.1 to more than 3 per 100,000 persons per year in both men and women with Asian populations generally at the lower and Western populations at the higher end [1]. The unique tumor biological feature of less than 1% tumor cells and a rich tumor microenvironment has in refractory patients proven ideal for drugs targeting not only tumor cells but also cells in the tumor microenvironment. In addition, the tumor cells are almost always positive for the tumor necrosis family receptor CD30, an ideal target for novel treatments. For many years, cHL has been staged into four stages according to the Ann Arbor classification and classified as having B symptoms or not. The staging principles are summarized in the Lugano Classification [2] and have been the basis for treatment decisions for decades. The different stages are often grouped into limited (stage IA-IIA) and advanced (IIB-IV) disease. At present, patients with limited disease at diagnosis are generally treated with 2-4 chemotherapy courses and involved-node radiotherapy and patients with advanced stages with 6-8 chemotherapy courses and sometimes additional radiotherapy. Chemotherapy used is mostly ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). The standard treatment for relapsed/refractory HL is salvage chemotherapy such as ICE (ifosfamide, carboplatin, etoposide) or DHAP (dexamethasone, high-dose Ara-C, cisplatin) followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT), but in some patients this is not tolerable, in others not sufficient for cure.

SURVIVAL OF PRIMARY REFRACTORY AND RELAPSED PATIENTS

To illustrate the efficacy of conventional treatment, the outcome in a population-based patient material from an earlier study [3] in the treatment era right before the introduction of targeted drugs was analyzed. In this cohort of Swedish HL patients 18-65 years, diagnosed between 1992 and 2009

with available clinical data (n=1429 patients), the 20-year overall survival (OS) was approximately 80% (Figure 1A). In the small group of 26 patients with primarily progressive disease (excluding 6 patients with deaths from/during treatment), OS was approximately 50%. (Figure 1B). Median time to death in the group of primarily progressive patients and patients with death during treatment combined was only 2.1 years [3]. In the cohort, 13% of the patients experienced a relapse with approximately 60% alive after 10 years (Figure 1C). The survival after an ASCT was also only approximately 60% despite chemo-sensitive disease (Figure 1D). The results in this recent Swedish material appear to be representative; historically, relapsing and refractory patients have, despite salvage chemotherapy and ASCT, a relatively poor outcome and approximately 50% of them experience additional recurrences and eventually die [4-6]. More use of allogeneic-SCT and better supportive care have however contributed to a longer median OS of the uncured patients since the year 2000 [3].

DRAWBACKS OF CONVENTIONAL THERAPY

Besides the occasional lack of efficacy, conventional chemo- and radiotherapy is also associated with long-term side-effects, such as secondary malignancies and cardiovascular diseases and subsequently risk of long-term sick leave and disability pension [7-10]. Particularly radiotherapy is affected by the risks of secondary malignancies [11] and cardiovascular disease [12]. A tailored approach in HL treatment has been the focus for the past 10-15 years with a reduction in the number of chemotherapy courses and limitation of irradiated volumes. These steps have resulted in less long-term morbidity, although the treatments used during the most recent decade are also associated with excess health care visits for patients versus matched comparators for a wide range of both somatic and psychiatric diagnosis (Glimelius and Eloranta et al, unpublished data). Despite the advancement in later years, the inherent effects of radiation and cytotoxic compounds will not eliminate adverse late effects for long.

INTRODUCTION OF TARGETED THERAPIES

The above described lack of efficacy in relapsed/refractory patients and the occurrence of late effects in the often young HL patients puts great demands on novel therapies. Until recently no new drugs were approved for these patients but years of basic research and better understanding of pathogenic mechanisms have finally provided us with a few. The antibody-drug conjugate brentuximab vedotin, Adcetris® targeting CD30 was approved in 2010 by the US food and drug administrator (FDA) and in October 2012 by the European Medicines Agency (EMA) and more recently an immune checkpoint inhibitor, nivolumab, Opdivo® was approved by FDA. These drugs are valuable complements to high-dose chemotherapy with allogenic-SCT for cure and as palliative treatments for others. Brentuximab vedotin is now moving into the first-line treatment in clinical trials, with the aim for even better outcomes, but are still awaiting the final results from these trials.

PATHOBIOLOGY OF CLASSICAL HODGKIN LYMPHOMA

Classical Hodgkin lymphoma (cHL) has distinctive and unique pathobiological features [13]. As mentioned above, less than 1% of the cells within involved lymph nodes consists of neoplastic cells. These are large and highly aberrant B-cells that sometimes are binuclear (as described by Dorothy Reed and Carl Sternberg) but more often mononuclear or multinuclear. The tumor cells are collectively called Hodgkin and Reed-Sternberg (HRS) cells and harbor the Epstein-Barr virus in approximately 30% in the western world. Most cells in the tumor mass are polyclonal T-cells, with variable numbers of eosinophils, neutrophils, B-cells, plasma cells, histiocytes and other cells, giving the background a reactive appearance.

The micro-environment of cHL has two important characteristics: 1. It strongly supports and stimulates the HRS cells and 2. It is ineffective in killing the tumor cells. The HRS cells use many different mechanisms to induce these two features. For example, they produce high amounts of the chemokine TARC (CCL17) that specifically attracts T-cells. The T-cells express tumor cell stimulating factors like tumor necrosis factor (TNF)-alpha and cluster of differentiation (CD)40 ligand that activate TNF receptors on the HRS cells, including CD40 and CD30, leading to continuous activation of the transcription factor nuclear factor kappa beta (NFkB). These and other HRS cell promoting signaling pathways can also be constitutively activated by mutations, although each of the mutation targets is affected in only a limited percentage of cases.

To escape from anti-tumor immune responses, the HRS cells apply many different mechanisms, such as expression of immunosuppressive cytokines, death inducing FAS and programmed death ligands PDL-1 and 2. In addition, HRS cells can lose expression of the human leukocyte antigen (HLA) that makes them unrecognizable to T-cells [14]. Most T-cells in the micro-environment are anergic CD4+ cells, which mostly resemble regulatory T-cells and T-helper (Th2) cells. The balance between dependence on the infiltrate and escape from immune responses may change over time, with increasing importance of the latter. However, the scarcity of Hodgkin cell lines indicates that HRS cells remain critically dependent on the micro-environment, with rare exceptions in patients with widespread end-stage disease.

MECHANISMS OF ACTION OF NOVEL TARGETED DRUGS

Treatment in cHL can be directed at the tumor cells and/or the micro-environment. The novel agent brentuximab vedotin (SGN-35) targets the CD30 molecule that is always expressed at high levels at the surface of HRS cells (Figure 2). It consists of a monoclonal anti-CD30 antibody that is conjugated to the cytotoxic compound monomethyl auristatin E (MMAE). Upon binding to CD30, the drug is internalized and the MMAE is released, causing disruption of microtubules and cell death. Of

note, occasional normal lymphocytes can also express CD30 if strongly activated, and these cells are present in normal lymphoid tissue and in the HL micro-environment. It is unknown to what extent these cells contribute to the therapeutic effect and/or unwanted side effects. The latter may also be induced by release of MMAE from dying cells into the circulation.

Another new approach uses, for example those targeting program death 1 (PD-1). PD-1 inhibitors may reactivate tumor specific T-cells, especially those that are inhibited by PDL-1 and PDL-2 that are virtually ubiquitously present on HRS cells. The proposed mechanism of action depends on recognition of non-self antigens that are presented in the context of HLA by the tumor cells. However, it is known that HLA is often down-regulated in HRS cells, especially in EBV-negative cases. It is possible though that PD-1 inhibitors may also have HLA independent therapeutic effects, e.g. by activating natural killer cells.

Another T cell activating therapy that circumvents the need for proper antigen presentation consists of T-cells with a chimeric antigen receptor (CAR T-cells). In this approach, cytotoxic T-cells from the patient are genetically engineered to recognize a receptor of choice. A chimeric gene that encodes for a specific antibody coupled to the intracellular signaling part of the T cell receptor is retrovirally transduced *in vitro* and these T-cells are then given back to the patient. In HL, CD30 would probably be the target receptor of choice, since it is the most consistent and specific cell surface marker, while B cell markers (including CD19) are generally lacking.

The Histone Deacetylase inhibitors (HDACs) affect multiple epigenetic mechanisms, including chromatin condensation and histone acetylation. This can induce differentiation, cell cycle arrest and apoptosis in malignant cells. In HL, it decreases production of the chemokine TARC. In addition, HDACs may induce anti-tumor effects by the micro-environment, by down-regulation of PD-1 on T-cells and opposing Th2 cell differentiation. In EBV+ cHL, HDAC inhibitors may induce a lytic EBV gene program, which should induce anti-EBV immune responses.

DESCRIPTION OF TRIALS OF NOVEL DRUGS AND RECENT ADVANCES IN TREATMENT

We searched Pubmed for articles on HL with the words “targeted therapy AND HL”, “brentuximab vedotin AND HL”, “PD-1 inhibitors AND HL”. All titles and abstracts were reviewed and all full-length clinical studies on brentuximab vedotin and PD-1 inhibitors were reviewed. In addition selected articles on “HDAC-inhibitors AND HL”, “mTOR inhibitors AND HL” and other “immunomodulatory drugs AND HL” were reviewed. Finally, abstracts presented at American Society of Hematology (ASH) in December 2015 and American Society of Clinical Oncology (ASCO) in June 2016 on HL were reviewed. The effects of targeted drugs on HL patients have also been the topic of a number of recent reviews, similar to this one, and these were also scrutinized to identify further clinical phase II and III trials of drugs with good response rates [6, 15-19]. Clinicaltrials.gov was studied for registered trials in July 2016.

ANTIBODIES

Antibody-drug conjugate brentuximab vedotin

Relapsed/refractory disease

When the anti-CD30 monoclonal antibody conjugated to MMAE, brentuximab vedotin, was approved by FDA in August 2011 for relapsed cHL after ASCT or after 2 prior chemotherapy regimens if ASCT was not tolerated, this was the first approval specifically for HL patients in a long time. In 2010, a phase I study of 45 patients reported that brentuximab vedotin induced tumor regression in most patients with CD30 positive relapsed/refractory lymphomas [20]. In 2012, Younes et al published the pivotal phase II trial of 102 patients, 15-77 years with refractory/relapsed HL and after an earlier ASCT. They reported that patients treated with 1.8mg/kg of brentuximab vedotin every 3 weeks for a maximum of 16 cycles showed an overall response rate (ORR) of 75% (95%CI 65-83%) (34% complete remissions (CRs)). Median progression-free survival (PFS) was 5.6 months (95%CI 5-9 months) and the median duration of response for those in CR was 20.5 months [21]. Three-year follow up showed

an OS rate of 73%, (95%CI 57-88%) and PFS rate of 58%, (95%CI 41-76%) [22]. OS at 5 years was 41%, (95%CI 31-51%) and PFS 22%, (95%CI 13-31%) (Figure 3, Table 1) [23].

Second-line

In a phase II study of 46 patients with relapsed/refractory HL after one previous doxorubicin-containing regimen, brentuximab vedotin resulted in 12 patients (27%, 95%CI 13-40%) achieving 18F-flourodeoxyglocose (FDG) positron emission tomography (PET)-negativity. PET-positive patients received additional treatment with augmented-ICE [24]. Overall 23 patients became PET-negative; these patients had much better 2-year event-free survival after ASCT than patients who did not achieve PET-negativity prior to ASCT. In 37 patients, Chen et al used brentuximab vedotin as second-line therapy *prior* to ASCT in relapsed/refractory HL patients and this resulted in an ORR of 68% (13 CR, 12 PR) and 32 patients (86%) proceeded to ASCT [25].

Consolidation

In 2015, the AETHERA study, a phase III trial evaluating brentuximab vedotin starting one to two months after ASCT as consolidation therapy, was reported [26]. Here 329 cHL patients with primary refractory disease or relapse within 12 months were randomized to treatment with active substance or placebo for up to 16 cycles. Brentuximab vedotin resulted in a significantly improved 2-year PFS compared with placebo (63% vs 51%, p=0.001). However, 32% of the patients could not fulfil treatment due to adverse events. Cross-over was allowed, and OS was similar. Updated results, presented at ASH in 2015, showed a 3-year PFS rate in the brentuximab vedotin arm of 61% (95%CI 53-68%) versus 43% (95%CI 36-51%) in the placebo arm (hazard ratio 0.52) [27] (Figure 3). In August 2015, FDA expanded the approval of brentuximab vedotin to also include its use as consolidation following ASCT in patients at risk of relapse or progression.

First-line

When brentuximab vedotin was tested in first-line as monotherapy in a phase II trial of 26 elderly patients (≥60 years), 52% reporting significant comorbidities, an ORR of 92% (73% CR) was seen, but the response duration was short (median 9 months, range 2.8-20.9) motivating the need for combination with other drugs. No correlation was observed between response and improvement in ECOG performance status [28]. At ASH in 2015, results were presented for 22 elderly patients treated with brentuximab vedotin in combination with dacarbazine and for 11 patients in combination with bendamustine. ORRs were 100% in both groups. The bendamustine dose had to be lowered from 90 to 70 mg/m^2 due to toxicity. With the dacarbacine combination, 18/21 remained alive without progression and 6 patients (36%) had ≥ grade 3 treatment-related adverse events [29].

Brentuximab vedotin has also been tested in first-line in a phase I trial with AVD or ABVD in 51 HL patients (median age 35, range 19-59) [30]. The latter proved to be too toxic, with fatal lung toxicity in two patients. Brentuximab vedotin was tested in combination with BEACOPP-like combinations in a phase II trial, including a total of 104 patients. Both the BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) and the BrECAPP (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, procarbazine, prednisone) schedules were highly active (CR rates 88% (95%CI 77-96%) and 86% (95%CI 73-94%) respectively) and feasible. The German Hodgkin Study Group has chosen BrECADD for further testing in a phase III trial against escalated BEACOPP for advanced stage HL, due to its superior toxicity profile [31]. In a phase II study, 41 limited stage patients were treated with ABVD followed by brentuximab vedotin consolidation rather than consolidation with radiotherapy. One death due to sepsis and hepatic failure was seen, considered caused by brentuximab vedotin. One year PFS and OS were 91% and 96%, respectively [32].

Other combinations with brentuximab vedotin and ongoing trials

Two studies have tested brentuximab vedotin 1.8 mg/kg with bendamustine, mostly using 90 mg/m^2 in relapsed/refractory patients [33, 34]. Feasible tolerability and high response rates

were reported at ASH, 2015. One trial combined brentuximab vedotin with donor lymphocyte infusion for the treatment of 13 relapsing patients after an allogenic-SCT and for 3 as consolidation; 10 of the 16 patients received the combination. Among the 13 patients with active disease, CR was seen in 7 and PR in 2 of them. Seven patients developed graft versus host disease (GVHD) [35].

Currently there are approximately 60 trials testing different combinations with brentuximab vedotin in HL patients in different clinical situations (clinical trials.gov July 2016). Combinations with mTOR inhibitors, HDAC inhibitors, PD-1 inhibitors, mentioned below, and other potentially active agents are ongoing [18]. The large phase III trials with brentuximab vedotin in first-line (for example ECHELON-1 and B-CAP, Figure 3) together with combination chemotherapy will be of great future interest. A way of rapidly testing potential efficacy of a drug like brentuximab vedotin in first-line is in a so-called window of opportunity trial [36]. The metabolic response by FDG-PET after a short treatment period prior to start of conventional standard chemotherapy could then be a surrogate marker of signs of activity, as in the study by Moskowitz et al [24]. The NCT 02275598 trial is also registered with this intention but has not started. It will however take decades before it is possible to evaluate the most interesting outcomes, i.e. long-term survival and freedom from severe late toxicity.

Side-effects

Brentuximab vedotin is generally well tolerated besides a high frequency of peripheral neuropathy (42%) [21]. Other side-effects are neutropenia, fatigue, pyrexia, diarrhea, nausea, arthralgia, peripheral motor neurophathy, and alopecia. As mentioned above, the combination with bleomycin should be avoided due to the risk of severe pulmonary toxicity [30]. A rarely reported side effect is multifocal leukoencephalopathy, a JC virus-induced central nervous infection [37], possibly due to depletion of CD30-expression activated T-cells. In addition, pancreatitis has been seen, likely due to unintended targeting of pancreatic CD30 positive cells and toxicity from MMAE [38].

Checkpoint inhibitors, PD-1 inhibitors

Nivolumab

PD-1 inhibitors can reactivate tumor specific T-cells, potentiating the T-cell anti-tumor activity. The PD-1 inhibitor nivolumab, a fully human monoclonal IgG antibody directed against PD-1, was recently introduced as therapy in relapsed/refractory HL [39]. The drug was given to 23 patients at a dose of 3 mg/kg every 2 weeks for a maximum of 2 years and an objective response was reported in as many as 20 patients (87%). Ten of them have had durable responses and in 7 of them, responses of over 1.5 years are seen [40]. Results from a phase II trial of 80 patients with relapse or progression who had received brentuximab vedotin and failed ASCT were recently published. The ORR was 66%, (95%CI 55-76%), 9% reached CR and 58% PR. Six months PFS was 77% [41]. In May 2016, Nivolomab was granted accelerated approval by FDA for treatment of cHL with relapse or progression after brentuximab vedotin and autologous SCT. Nivolumab also gave a high ORR of 75% in 16 evaluable patients treated within a Japanese phase II trial of relapsed/refractory patients previously treated with brentuximab vedotin [42]. For nivolumab, 8 trials are currently registered on clinical trials.gov, HL patients only are included in four of them. In all others HL patients represent one among many tumor types.

Side effects

Adverse events reported from nivolumab were not life threatening but included decreased lymphocyte and platelet counts, increased serum lipid levels, myelodysplastic syndrome and immune-related side effects such as pancreatitis, pneumonitis, stomatitis and colitis. Adverse events commonly associated with PD-1 inhibition used for solid malignancies are also pruritus, rash and diarrhea. More uncommon side effects include immune mediated pneumonitis, colitis, hepatitis, hypophysitis and thyroiditis [43]. The side effects can be decreased with corticosteroids and infliximab [44]. In a phase I study of nivolumab for relapsed/refractory disease from other hematological malignancies including 88 patients, 12 patients (15%) discontinued treatment due to adverse events while fatal pneumonitis occurred in one patient (previously having received nine

systemic treatment regiments). Other side effects of any grade were fatigue (17%), decreased appetite, pruritus, rash (all 9%), diarrhea and pyrexia (7%) [45].

Patients with a history of an allogenic-SCT were initially excluded from treatments targeting PD-1 due to concerns of GVHD. The efficacy and toxicity of nivulomab in 8 HL patients relapsing after allogenic SCT were evaluated, median time from allogenic SCT to nivolumab treatment was 11 months, range 3-122 months. Acute GVHD occurred in 2 patients, 7 out of 8 had clinical benefit, and the authors concluded that the drug is effective with manageable toxicity but that the experience is limited and prospective trials are needed [46]. Treatment with pembrolizumab, further discussed below, in 2 patients after allogenic-SCT was well tolerated and not associated with reactivation of GVHD [47]. In transplanted patients without active GVHD, treatment with PD-1 inhibitors are now considered safe without major risk of GVHD activation [12, 47].

Pembrolizumab

Another PD-1 inhibitor, pembrolizumab**,** also a humanized IgG4 antibody against PD-1 on T-cells has been administrated in doses of 10mg/kg every 2 weeks in 31 patients with an ORR of 65% (48%-79%). Sixteen percent reached CR and 48% reached PR. Seventy percent of the responses lasted longer than 24 weeks [48]. In a phase II trial using pembrolizumab, presented at ASCO 2016 [49], 3 cohorts were treated: (i) relapsed/refractory HL after ASCT and brentuximab vedotin; (ii) patients ineligible for autologous SCT due to chemo-resistance (no response to salvage chemotherapy) and brentuximab vedotin failure and (iii) relapsed/refractory cHL after ASCT but not treated with brentuximab vedotin. Interim results in the 30 patients in cohort one showed an ORR of 70% (95%CI 51-85%). The ORR among the 30 patients in cohort 2 was 80%, (95%CI 61-92%). Pembrolizumab is not approved at the time of writing but will be sent to FDA in September 2016. For pembroluzimab, seven ongoing or just completed trials are registered on clinical trials.gov, four for HL patients only and three with other tumor types also included. Pembrolizumab appears to give similar results as nivulomab regarding efficacy, duration of response and side-effects [48].

How to handle PD-1 responding patients?

Whether the PD-1 inhibitors have a curative potential with durable responses beyond two to three years is not currently known. It is also unknown what the best strategy is in patients who respond to the drug. A recent review has tried to identify the available options that exist in this clinical situation and presents arguments to aid clinical decision making [50]. The options they present for patients responding to PD-1 inhibitors are:

1. Continuation of therapy,
2. Cessation of therapy with potential retreatment,
3. Continue to a transplantation,
4. Chimeric antigen receptor T-cell therapy (within a clinical trial).

To continue with therapy is possibly most suitable for non-fit patients due to the unclear curative potential. To stop therapy after having achieved CR with the possibility of repeated treatment is less burdensome for the patients and less costly, but has the risk of potential failure at retreatment. One patient was successfully retreated with nivolumab after a relapse 43 weeks after the initial treatment had stopped and achieved a second CR [40]. To consider a SCT (most likely an allogenic SCT since the present indication for PD-1 inhibitors is relapse after an autologous SCT), may be considered for young fit patients. If done soon after finishing PD-1 therapy, this could however increase the risk of GVHD, veno-occlusive disease and febrile illness [51]. The forth option mentioned is to proceed to CAR T-cell therapy, although this has to be done within trials.

CHIMERIC ANTIGEN RECEPTOR T-CELLS

Another way to overcome the immune blockade seen in HL tumors is to use CAR T-cells. These cells targeting the tumor cells have shown promising results in trials for other lymphomas. Bollard treated 25 patients with anti-EBV CAR Ts and noticed an ORR of 50% [52]. Now a next generation of CAR T-cells is being investigated. Ten clinical trials are currently (July 2016) registered at clinicaltrials.gov also including HL patients, six of them are actively recruiting patients. The majority use CD30 directed

CAR T-cells since the HRS almost exclusively are CD30 positive. The therapies have instilled hope for therapy refractory patients, however the CAR T-cell therapy have been associated with side-effects with cytokine release syndrome since cells other than the malignant B-cells are also targeted. In other lymphomas combinations trials with CAR T-cells and immune checkpoint inhibitors are tested.

HDAC INHIBITORS, mTOR INHIBITORS, OTHER IMMUNOMODULATORY DRUGS

Another group of targeted drugs, actually developed for relapsed/refractory HL prior to brentuximab vedotin and the PD-1 inhibitors, is the histone deacetylase (HDAC) inhibitors. They did not produce as many remarkable responses as brentuximab vedotin and the PD-1 antibodies did, but have resulted in comparable PFS [18]. In 129 relapsed/refractory HL patients treated with the HDAC inhibitor panobinostat 40mg orally three times a week as monotherapy, tumor size reduction was seen in 96 patients (74%). The ORR was 27%, 30 with PR and 4 with CR. Median PFS was 6.1 months [53]. In a phase I trial, panibinostat and the mammalian target of rapamycin (mTOR) inhibitor everolimus were combined in 14 relapsed/refractory patients with an ORR of 43% [54]. Adverse events were significant thrombocytopenia. In a heavily pretreated female patient, a combination of the pan-histone deacetylase inhibitor vorinostat and the mTOR inhibitor sirolimus, rapamune produced a remarkable response bridging the patient to an allogenic SCT and potential cure [55]. A phase II trial of the mTOR inhibitor everolimus in 19 relapsed HL patients showed an ORR of 47% (95%CI 24-71%), one with CR [56]. The immunomodulatory drug lenalidomide also has effect in HL [57, 58]. The interest in HDAC inhibitors, mTOR inhibitors and immunomodulatory drugs has declined since the introduction of brentuximab vedotin and PD-1 inhibitors due to less effectiveness/more side-effects but they could find a role in combination therapies.

Other novel drugs, for example another immune checkpoint inhibitor lymphocyte-activation gene-3 (LAG-3) and anti-PDL1 antibodies, are promising by either blocking the typical immune suppression in HL tumors or inducing immune stimulation in the tumors. Drugs targeting

deregulated pathways in the HRS-cells, like combinations of PI3Kδ and JAK-1 inhibitors, are also being explored and claim to be promising [19].

FUTURE DEVELOPMENTS AND CONCLUDING REMARKS

No other drug had received FDA approval for treatment of patients with HL since 1977 when brentuximab vedotin was approved in 2011, making this the start of a new era. Today brentuximab vedotin can be used in refractory patients improving the chances for the patient to e.g. be eligible for an allogenic SCT, however it is yet to be defined when this drug will provide its best benefit (in first-line, second-line, as consolidation and/or in refractory disease/relapse). If brentuximab vedotin moves into the first-line situation, new trials besides the ATHERA study will be needed to show if it still has an advantage as consolidation therapy. The OS results of the ATHERA study are also eagerly awaited but will not be presented until 2020.

The apparently efficient PD-1 inhibitors have rapidly moved into clinical trials of refractory patients in many malignancies, including HL. When nivolumab was approved for relapsed HL patients after an autologous SCT and failing brentuximab vedotin in May 2016, not only a second drug was approved since 1977, but this also points to a new fascinating and expanding era where the tumor cells are not the primary target.

We are witnessing an explosion of ongoing trials not only in relapsed/refractory patients but also for patients earlier in the disease. The “race” between the medical drug companies towards obtaining approval for their particular drug is hopefully of benefit to individual patient not only experiencing refractory/relapsed disease but in the future also for early/earlier disease. Today, only results from phase I and II trials presented at international meetings, such as ASH and ASCO, and single full length publications exist and results from phase III trials are generally lacking. More trial results are needed before these drugs and combinations of drugs can be used upfront and also be available throughout the world.

The explosion of new drugs not only in a rather uncommon malignancy such as HL, but also in much more common malignancies, will put significant pressure on health resources, and they must be used most efficiently. Most, or all new drugs, have a high financial price. Part of this is due to the high development costs for the new drugs, and the large phase III trials constitute the most expensive aspect of development for the companies. Accelerated approval based upon phase II trials only, could at least potentially result in lower prices of the drugs. However, this has to be weighed against the risk of this procedure.

Even though the prognosis is generally favorable in HL, the few patients who are primarily progressive/or relapse have a rather poor survival, confirmed also in this investigation. If the novel drugs can bridge these few resistant individuals to an allogenic-SCT and an eventual cure, that implies a tremendous advantage. However for the majority of HL patients, the great challenge today is not to reach cure with the available drugs, but rather to prevent late side effects of present treatments. Brentuximab vedotin has moved into first-line trials, evaluating its efficacy in replacing radiotherapy in limited stages and the most toxic chemotherapy in advanced stages. In the elderly/fragile patients, it may, if the early promises hold, substantially reduce toxicity and add more good years of life. However, the toxicities from at least some of the novel drugs are not negligible, and we have absolutely no information about long-term late toxicity. Late effects are a problem for the often young patients at diagnosis and when novel targeted drugs are introduced long and detailed follow-up is of utmost importance.

For obvious reasons, no large population-based studies yet exist that evaluate the effects of the introduction of the novel targeted drugs. One attempt was presented as ASCO with 136 patients included, 69 (51%) having relapsed or progressed after ASCT. Of those patients 40% were exposed to at least one or more novel agents after relapse including 34% receiving brentuximab vedotin, 9% nivolumab and a few also lenalidomide and panobinostat. Median OS was 34 months. Patients treated with novel agents had a prolonged OS compared with patients treated with

conventional chemotherapy (86 vs 22 months, p=0.007) [59], but likely selection bias was present, with the healthiest patients receiving the novel drugs.

Further studies are needed to investigate the biological actions of the drugs and to find and validate predictive markers. For this, systematic gathering of tumor material at diagnosis and at relapse and collection of clinical data in national and international collaborations is essential. It will be important to allow detailed and long-term follow-up of the completed and currently running trials and in large population-based investigations.

Author's disclosure of potential conflicts of interest

Arjan Diepstra is a member of the Takeda scientific advisory board on minimal residual disease in Hodgkin lymphoma. Ingrid Glimelius has no potential conflicts of interest.

FIGURE LEGENDS

Figure 1 Kaplan-Meier curves were used to illustrate overall survival in patients with Hodgkin lymphoma 18-60 years diagnosed in Sweden 1992-2009 (during the era of pre-targeted drugs) illustrating the need of novel treatment concepts. **A**. Top panel left column: overall survival for all patients. **B**. Top panel right column: overall survival for patients with primary progressive disease (n=26, defined as progressive disease during treatment, relapse or death with or from HL within three months after finished primary treatment). Patients with toxic deaths n=6 were not included in the analysis. Follow-up starts 6 months post-diagnosis. **C**. Bottom panel left: Overall survival of all patients post relapse irrespective of relapse treatment. Follow-up starts at the time of relapse. **D**. Bottom panel right: Overall survival for all patients going through an autologous stem cell transplantation (ASCT) for primarily progressive disease or relapse. Follow-up starts at the date of transplantation.

Figure 2 Mechanisms of action of novel targeted drugs. **Brentuximab Vedotin** is a monoclonal antibody that targets CD30 and that carries the cytotoxic compound MMAE. MMAE is released upon endocytosis and induces microtubule disruption. **Checkpoint inhibitors** are monoclonal antibodies that block inhibitory receptors on cytotoxic T cells from the patient, e.g. PD-1. Upon recognition of non-self antigens that are presented in the context of HLA class I, the activated cytotoxic T cells kill the tumor cell. **CAR-T** cells are patient derived cytotoxic T cells that are genetically engineered to express a chimeric receptor that recognizes a tumor cell specific target, e.g. CD30, resulting in T cell activation and cytotoxic killing. **HDAC inhibitors** affect histone acetylation and chromatin condensation, thereby inducing differentiation and apoptosis. In addition, these inhibitors can down regulate PD-1 on T cells. They also decrease production of TARC and oppose differentiation of T cells to Th2 cells, which should decrease the number of immune suppressive Th2 and Treg cells in the micro-environment.

Abbreviations figure 2:

B2M = beta-2-microglobulin, CAR = chimeric antigen receptor, HDAC-i = Histone Deacetylase inhibitor, HLA-I = Human Leukocyte Antigen class I, MMAE = monomethyl auristatin E, PD-1 = programmed death 1, PDL-1 = programmed death ligand 1, TARC = Thymus and Activation Related Chemokine.

Figure 3 Overview of published phase II and III studies, including abstracts (pubmed, ASH 2015 and ASCO 2016) on treatment with brentuximab vedotin (upper part of the figure) and the immune checkpoint inhibitors nivolumab and pembrolizumab (lower part of the figure) for Hodgkin lymphoma and selected ongoing trials. Studies are presented according to which treatment line they are tested in and outcome results of included studies are presented in Table 1. The current approvals (August 2016) are indicated in the shaded boxes.

Abbreviations figure 3 and table 1:

N=Number of included patients, BV=Brentuximab vedotin, Yr=Year, n=number, BrECADD= brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone, BrECAPP= brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, procarbazine, prednisone, CI=Confidence Interval, ASH=American Society of Hematology, ABVD= adriamycin, bleomycin, vinblastine, and dacarbazine, RT=radiotherapy, PFS=Progression Free Survival, ASCO= American Society of Clinical Oncology, AVD=adriamycin, vinblastine, and dacarbazine, B-CAP=Brentuximab vedotin, cyclophosphamide, doxorubicine, predniso(lo)ne, escBEACOPP=escalated BEACOPP, including bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone, PET=Positron Emission Tomography, ORR=Overall Response Rate, ASCT=Autologous Stem Cell Transplantation, OS=Overall Survival, PFS=Progression Free Survival, CR=Complete Remission, PR=Partial Remission, ISRT=Involved site radiotherapy, Gy=Gray

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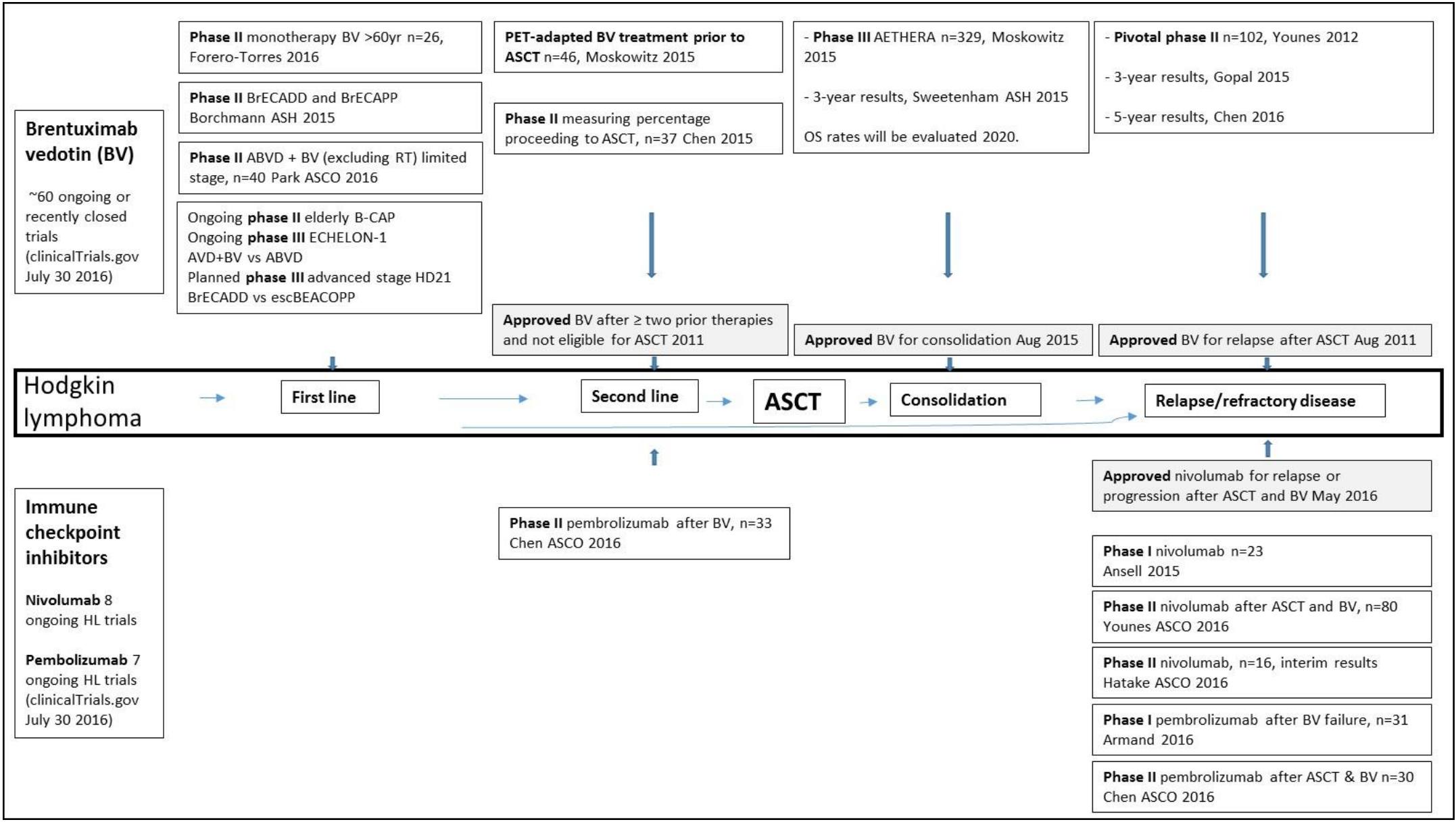
Table 1

Drug/combination	Treatment line	Phase	N	Outcome	Author, journal, year
Brentuximab Vedotin (BV)	**Relapse/refractory**				
Pivotal	Relapse/refractory	II	102	ORR 75%, 95%CI: 65-83 PFS 5.6 months	Younes J Clin Oncol 2012
3-year		II	102	OS 73%, 95%CI 57-88% PFS 58%, 95% 41-76%	Gopal, Blood 2015
5-year		II	102	OS 41%, 95%CI 31-51%	Chen Blood 2016
	Consolidation				
Pivotal (AETHERA) BV 16 cycles vs placebo	Consolidation post ASCT in unfavorable risk relapsed patients or primary refractory	III	329	PFS 43 months, 95%CI 30-43 (BV) versus 24 months 95%CI 36-51% (placebo), OS similar	Moskowitz Lancet 2015
3-year (AETHERA)		III	329	PFS rate 61% 95%CI 53-68% (BV) vs 43%, 95%CI 36-51% (placebo) OS results will be presented 2020	Sweetenham ASH 2015
	Second line				
PET-adapted BV	Second line	II	46	N=12 (27%) 95%CI 13-40% became PET-negative after BV	Moskowitz Lancet Oncol 2015
BV prior to ASCT	Second line	II	37	ORR 68%, 86% proceeded to ASCT	Chen Biol Blood Marrow Transpl 2015
	First line				
BV+ABVD/ BV+AVD	First line	I	51	Serious events in 14 (56%) if combined with ABVD and 7 (27%) if combined with AVD, severe pulmonary toxicity with ABVD	Younes Lancet Oncol 2013
BV monotherapy elderly >60 years	First line	II	26	ORR 92% (73% CR), median response only 9.1 months (range 2.8+-20.9+), peripheral sensory neuropathy (78%)	Forero-Torres Blood 2016
BV combinations with BEACOPP	First line	II	104	BrECADD: CR 88%, 95%CI 77-96% BrECAPP: CR 86%, 95%CI 73-94%	Borchman ASH 2015
ABVD + BV consolidation (no RT)	First line limited stage	II	40	1-year PFS 91%	Parc ASCO 2016, abstract 7508
4 (BV + AVD) if PET negative 30Gy ISRT	First line limited stage, unfavorable	Pilot	30	2 patients PET positive – off study, 1-year PFS 93% (95%CI 84-102). No pulmonary toxicity.	Kumar Blood 2016
Checkpoint inhibitors	**Relapse/refractory**				
Nivolumab	Relapsed/refractory	I	23	ORR 87%, 95%CI 66-97	Ansell N Engl J Med 2015

Nivolumab	Relapsed/refractory after ASCT and BV	II	80	ORR 66%, 95%CI 55-76	Younes ASCO 2016, abstract 7535
Nivolumab	Relapsed/refractory after BV	II	16	ORR 75%, 95%CI 48-93	Hatake ASCO 2016, abstract: e19018
Pembrolizumab	Relapsed/refractory after BV failure	I	31	ORR 65%, 90%CI 48-79	Armand J Clinical Oncol 2016
Pembrolizumab	Relapsed/refractory after ASCT and BV	II	30	ORR 70%, 95%CI 51-85	Chen ASCO 2016, abstract 7555
	Second line				
Pembrolizumab	Second line after BV	II	33	ORR 80%, 95%CI 61-92	Chen ASCO 2016, abstract 7555


Brentuximab vedotin (BV)
~60 ongoing or recently closed trials (clinicalTrials.gov July 30 2016)
Phase II monotherapy BV >60yr n=26, Forero-Torres 2016
Phase II BrECADD and BrECAPP Borchmann ASH 2015
Phase II ABVD + BV (excluding RT) limited stage, n=40 Park ASCO 2016
Ongoing phase II elderly B-CAP
Ongoing phase III ECHELON-1 AVD+BV vs ABVD
Planned phase III advanced stage HD21 BrECADD vs escBEACOPP
PET-adapted BV treatment prior to ASCT n=46, Moskowitz 2015
Phase II measuring percentage proceeding to ASCT, n=37 Chen 2015
- Phase III AETHERA n=329, Moskowitz 2015
- 3-year results, Sweetenham ASH 2015
OS rates will be evaluated 2020.
- Pivotal phase II n=102, Younes 2012
- 3-year results, Gopal 2015
- 5-year results, Chen 2016
Approved BV after ≥ two prior therapies and not eligible for ASCT 2011
Approved BV for consolidation Aug 2015
Approved BV for relapse after ASCT Aug 2011
Hodgkin lymphoma
First line
Second line
ASCT
Consolidation
Relapse/refractory disease
Immune checkpoint inhibitors
Nivolumab 8 ongoing HL trials
Pembolizumab 7 ongoing HL trials (clinicalTrials.gov July 30 2016)
Phase II pembrolizumab after BV, n=33 Chen ASCO 2016
Approved nivolumab for relapse or progression after ASCT and BV May 2016
Phase I nivolumab n=23 Ansell 2015
Phase II nivolumab after ASCT and BV, n=80 Younes ASCO 2016
Phase II nivolumab, n=16, interim results Hatake ASCO 2016
Phase I pembrolizumab after BV failure, n=31 Armand 2016
Phase II pembrolizumab after ASCT & BV n=30 Chen ASCO 2016